Executive Summary

Background

The mechanisms by which particulate matter (PM) exposure disrupts cardiac function and worsens cardiovascular disease (CVD) are not well understood. There is a growing body of knowledge that suggests that PM exposure can induce inflammatory changes in blood vessels and exacerbate atherogenesis leading to the development of atherosclerotic plaques and lesions. We hypothesized that PM exposure would abnormally activate endothelial cells and induce vascular inflammation that will lead to the accelerated formation of arterial plaques which are a hallmark of atherosclerosis.

Methods

The study was performed using mice that were genetically susceptible to the development of atherosclerosis. The mice were exposed to concentrated ambient fine particles ($PM_{2.5}$) for 4 days per week, 6 hours per day for 6 months. The exposure concentrations averaged about 160 $\mu g/m^3$. We examined several factors relevant to mechanisms of atherogenesis and the development of cardiovascular heart disease. The development of atherosclerosis was monitored over the course of exposures using an ultrasound microscope technique. Mechanistic endpoints that were evaluated included plasminogen activation inhibitor-1 (PAI-1), which is an acute-phase reactant that can become transiently elevated by inflammation and plays a role in atherothrombosis; soluble forms of the intercellular, vascular and endothelial cell adhesion molecules ICAM-1, VCAM-1 and E-selectin, that are postulated to play a role in development of atherosclerotic plaque; matrix metallopeptidase-9 which is involved in tissue remodeling associated with inflammatory disease processes; and C-reactive protein, which is produced in the liver and is an acute phase proteins that increase during systemic inflammation. In addition, we measured the effects of exposure on cardiac function in a subset of the mice that were implanted with cardiographic transponders. Heart rate, heart rate variability and arrhythmias were determined. Frozen samples of aortic arch were

reserved for analysis of biomarkers associated with oxidative stress including defensive molecules (glutathione and heme-oxygenase) and for protein carbonyls as a measure of oxidative damage.

Results

The results of this study show that $PM_{2.5}$ exposure (160 μg/m^3) accelerated the development of atherosclerotic plaque in genetically susceptible mice approximately 1.6-fold compared to plaque development in mice exposed to purified air ($p \leq 0.05$). The concentration of CRP in plasma was significantly correlated with plaque development in PM-exposed mice but not in air-exposed mice. It is important to note that the mice used in this study were fed a normal chow diet. We can compare our results with a study using similar methods of exposures and endpoints that were performed using mice exposed in New York that were fed either a standard rat chow diet or a high fat (so-called Western) diet by researchers at New York University. In contrast to our study of mice exposed to ambient air in Riverside, CA, the NYU study showed significant results only for the mice fed a high fat diet. It is not possible to rule out that the reason that we observed a significant PM-related increase in atherosclerosis development in mice fed a normal diet while significant PM-related effects were seen in the high fat group in the NYU study was that a higher PM concentration was used in our study (160 μg/m^3) than in the NYU study (85 μg/m^3).

Conclusions

We conclude that subchronic exposure to elevated concentrations of $PM_{2.5}$ will potentiate the development of atherosclerosis. An earlier study at NYU demonstrated significant increases in plaque formation in genetically susceptible mice after exposure to concentrated $PM_{2.5}$ compared to mice exposed to purified air. In general our results confirm those of this earlier NYU study, however the mice in our study were fed a standard chow diet whereas the NYU group showed significant changes only in mice fed a high fat diet. This might be due to differences in the sources of air pollution between New York and Riverside, CA. We also demonstrated that C-reactive protein in plasma,

which is an indicator of systemic inflammation, may be a useful biomarker for risk of development of atherosclerosis.